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Previews

# TOR Signaling and S6 Kinase 1: Yeast Catches Up

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**Conservation of the rapamycin-sensitive TOR signaling network among eukaryotes has been instrumental to the rapid progress made in this field in recent years. A recent report in *Molecular Cell* (Urban et al., 2007) now extends this conservation to include Sch9, an AGC protein kinase family member from *S. cerevisiae*, which appears to be the long sought after yeast ortholog of mammalian S6 kinase 1 (S6K1) and a direct target for the rapamycin-sensitive TOR complex I.**

The TOR (target of rapamycin) signaling network represents an important mechanism by which cell growth is coupled to extracellular cues, including nutrient availability, in all eukaryotic organisms examined to date (Wullschleger et al., 2006). This network was discovered through the action of rapamycin, an immunosuppressant and anticancer drug that inhibits the activity of the large, evolutionarily conserved TOR kinase, a member of the PI3-like kinase family of serine/threonine protein kinases. TOR assembles with a number of other proteins to form two distinct protein complexes, termed TOR complex 1 and 2 (TORC1 and TORC2), of which TORC1 is uniquely inhibited by rapamycin. Present models suggest that TORC1 and TORC2 independently regulate distinct growth-related processes—for example, ribosome biogenesis and cytoskeletal organization, respectively—and thereby collaborate to control both temporal as well as spatial aspects of cell growth (Wullschleger et al., 2006).

A unique interplay has existed over the years with respect to results obtained in the budding yeast *S. cerevisiae* and higher eukaryotic systems and has proven crucial to our present understanding of the architecture of the TOR network. For example, through the isolation of mutations that confer dominant rapamycin resistance, yeast genetics led to the initial discovery of Tor1 and Tor2, the two TOR homologs in yeast (Wullschleger et al., 2006). Subsequent biochemical approaches led to the identification of a single mammalian ortholog, mTOR. The fact that yeast possesses two TOR kinases and that Tor2, but not Tor1, is essential allowed for detailed genetic analyses that revealed that Tor2 participates in a second essential cellular activity that is not sensitive to rapamycin (Wullschleger et al., 2006). This Tor2-specific and rapamycin-insensitive function was initially chalked up to being an oddity of yeast physiology. In retrospect, however, this early discovery paved the way for thinking about TOR as being involved in multiple functions and presaged the identification of distinct TORC1 and TORC2 complexes in both yeast and mammals.

On the other hand, there has been somewhat of a disconnect with respect to the identity of target proteins directly phosphorylated by TOR in yeast versus mammals. Perhaps the most well-known example involves phosphorylation of S6 kinase 1 (S6K1) by mammalian TORC1 (mTORC1). S6K1 is a member of the AGC family of protein kinases (named for their similarity to protein kinases A, G, and C) (Dann et al., 2007). Full activation of S6K1 requires phosphorylation of sites within a so-called hydrophobic motif (HM) by mTORC1 as well as phosphorylation within its activation loop by phosphoinositide-dependent kinase 1 (PDK1) (see Figure 1). Activated S6K1 recognizes a number of downstream targets, including ribosomal protein S6 (RPS6) (hence its name). Many years ago, phosphorylation of RPS6 was shown to correlate with translation of mRNAs that contain 5′TOP (terminal oligopyrimidine) structures, including mRNAs that encode ribosomal proteins. In a scenario that had become well entrenched in the literature, it was hypothesized that mTORC1 regulates ribosome biogenesis in mammalian cells at the level of protein synthesis via activation of S6K1, phosphorylation of RPS6, and, ultimately, translation of 5′TOP mRNAs (Thomas and Hall, 1997). By contrast, an analogous system did not appear to operate in yeast (where, for example, there are no 5′TOP mRNAs), and TORC1 has instead been shown to regulate ribosome biogenesis at the level of transcription (Wullschleger et al., 2006). Moreover, no convincing homolog of S6K1 could be identified in yeast. Now that the link between S6K1 activation and 5′TOP translation has been thrown into serious doubt (see Dann et al., 2007 and references therein), the question has resurfaced as to whether an mTORC1-S6K1 branch might be conserved in yeast after all.

Enter Sch9, one of several AGC kinases that have been identified in yeast. Previous studies have demonstrated that this protein is involved in nutrient-dependent control of cell growth and, moreover, that its phosphorylation state is responsive to rapamycin treatment; however, its precise connection to TOR signaling remained unclear (Jorgensen et al., 2004). The recent study by Loewith and coworkers (Urban et al., 2007) significantly extends these findings with the demonstration that there are several sites within the C-terminal region of Sch9, including sites corresponding to an HM motif, that are phosphorylated directly by TORC1 in vitro and

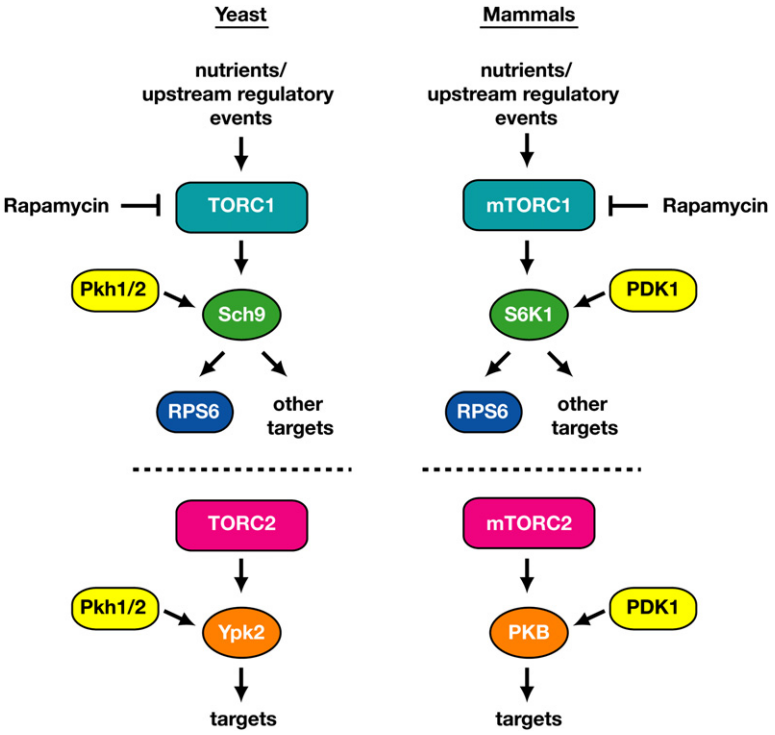


**Figure 1. A Model for Conservation of the TOR Signaling Network in Yeast and Mammals**
See text for details.

that these correspond to the major rapamycin-sensitive phosphorylation sites in vivo. By constructing mutant forms of Sch9 that correspond to hyper- or hypophosphorylated mimics, the authors were able to attribute a number of TORC1-specific readouts (e.g., ribosome biogenesis and translational initiation) as being directly influenced by Sch9. And yes, Sch9 was shown in this study to directly phosphorylate RPS6. Finally, additional experiments revealed that there is an independent phosphorylation event within the activation loop of Sch9 by Pkh1, a yeast ortholog of PDK1. In total, these experiments place Sch9 in a pathway that appears to be very analogous to S6K1 (Figure 1).

This work by Urban et al. (2007) is important in that it identifies what is likely to be the first bona fide substrate for TORC1 in yeast and will therefore provide an important handle for dissecting TORC1 function further in this organism. However, this conclusion is likely to generate some controversy, as Sch9 has also garnered attention as being the likely yeast ortholog of mammalian PKB (also known as Akt), an AGC kinase implicated in cell growth regulation and cancer progression (Sobko, 2006). In mammalian cells, PKB/Akt has long been implicated in mTOR signaling; however, its precise place within the pathway was difficult to pinpoint. This confusion has been largely resolved with the discovery of two mTORCs and findings by Sabatini and coworkers (Sarbassov et al., 2005) that PKB/Akt is a direct target for mTORC2. Thus, the model that has emerged is that mTORC1 cooperates with PDK1 to activate S6K1, whereas mTORC2 cooperates with PDK1 to activate PKB/Akt (Dann et al., 2007). A similar scenario can now be established for yeast (Figure 1). For example, Urban et al. have demonstrated that Sch9 does not serve as a substrate for TORC2, at least in vitro. By contrast, a distinct AGC kinase, Ypk2, has been shown to be a direct target for TORC2, and this activation step is required for actin polarization and cell viability (Kamada et al., 2005). Thus, activation of distinct AGC kinases via direct phosphorylation by the two TORCs emerges as a theme that is conserved in both yeast and mammals.

Interestingly, both Tor1, which assembles exclusively into TORC1, and Sch9 have been identified recently as influencing life span in response to caloric restriction in yeast (Kaeberlein et al., 2005). As pointed out by Urban et al. (2007), it is possible that the mTORC1-S6K1 cassette may also turn out to play a role in life-span regulation in higher eukaryotes. In other words, the mammalian TOR field may have some catching up to do of its own.

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